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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,878	01/16/2004	Samuel Jotham Reich	129402.00701	1285

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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,878	REICH ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59 and 75-87* is/are pending in the application.

4a) Of the above claim(s) *1-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-59 and 75-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :November 7, 2006 and January 5, 2007.

DETAILED ACTION

This Office Action is a response to Applicant's Amendment and Remarks filed February 26, 2007.

Claims 60-74 have been canceled. New claims 78-87 are acknowledged.

Claims 1-59 and 75-87 are pending in the instant application.

Claims 1-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on August 14, 2006.

Claims 32-59 and 75-87 have been examined on the merits.

This application contains claims 1-31 drawn to an invention nonelected with traverse in the reply filed on August 14, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

Applicant's information disclosure statements filed November 7, 2006 and January 5, 2007 are acknowledged. The submissions are in compliance with the provisions of 37 CFR §1.97. Accordingly, the Examiner has considered the information disclosure statements and signed copies are enclosed herewith.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed August 25, 2006, claims 32-77 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is moot** against claims 60-74 in view of Applicant's Amendment to cancel these claims, filed February 26, 2007. **This rejection is withdrawn** against claims 32-59 and 75-77 in view of Applicant's Amendment to the claims, filed August 14, 2006. Specifically, the Examiner is withdrawing this rejection in view of Applicant's Amendments to the claims to remove language referring to methods of using siRNAs targeted to mutant or cognate forms of human ICAM-1.

In the previous Office Action mailed August 25, 2006, claims 32-77 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. **This rejection is moot** against claims 60-74 in view of Applicant's Amendment to cancel these claims, filed February 26, 2007. **This rejection is maintained** against claims 32-59 and 75-77 for the reasons of record set forth in the previous Office Action mailed August 25, 2006. It is noted that new claims 78-87 are also included in this rejection.

Response to Arguments

In response to this rejection, Applicants argue that under 35 U.S.C. § 112, first paragraph, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Applicants also argue that the test of enablement is whether one reasonably skilled in the art could

make and use the invention from the disclosures in the specification coupled with the information known in the art, without undue experimentation. Applicants rely on *In re Wands*. Applicants contend that the instant application teaches how to choose target sites in human ICAM-1, how to make siRNA molecules, how to use the siRNA molecule, and how to deliver the siRNA. Applicants point the Examiner to specific pages and paragraphs in the instant specification. Given these teachings, Applicants contend that only routine experimentation would be required to make and use siRNA molecules in the methods claimed.

Applicant's arguments and contentions have been fully considered, but are not found persuasive. First, the Examiner agrees, under 35 U.S.C. § 112, first paragraph, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Second, the Examiner also agrees that the test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the specification coupled with the information known in the art, without undue experimentation. However, a review of the instant application finds working examples directed to the inhibition of human ICAM-1 expression and cytotoxicity profiles in HEK 293 (*in vitro*) following the administration of siRNAs targeted to human ICAM-1. The instant claims are directed to methods of inhibiting the expression of human ICAM-1 and methods of treating complication arising from type I diabetes in a subject (*in vivo*) following the administration of siRNAs targeted to human ICAM-1. No exemplary disclosure is provided regarding the therapeutic use of the claimed methods for targeting and inhibiting human ICAM-1 in living organisms,

including any mammal, using siRNA. As the previous references of Lu et al., Samarsky et al., and Downward et al indicate, cell culture results are not readily extrapolated to *in vivo* applications.

While Applicants teach broad prophetic technical disclosures regarding the therapeutic use of siRNA for targeting and inhibiting human ICAM-1 in living organisms, including any mammal, such a disclosure would not be considered enabling since the state of siRNA-mediated gene inhibition is highly unpredictable as detailed in the previous Office Action mailed August 25, 2006 at pages 11-13. Therefore, using the prophetic disclosures in the specification, coupled with the information known in the art regarding the known unpredictability of using siRNA *in vivo*, one reasonably skilled in the art would not be able to make and use the invention without undue experimentation. Given the fact that the instant disclosure fails to teach or provide specific [not broad and obtuse] information regarding *in vivo* siRNA specific mode of treatment, delivery route, concentration, tissue specificity, etc., one reasonably skilled in the art would not deem this experimentation as routine.

Applicants also argue that while the instant specification teaches prophetic examples, such examples are permitted to support the application and claims. Applicants point the Examiner to MPEP 608.01(p). Applicants argue that the *in vitro* methods of inhibiting human ICAM-1 expression demonstrate the efficacy or ability of the siRNA to silence human ICAM-1 mRNA upon administration to the cell, in combination with the general state of the art with respect to the *in vivo* delivery of siRNA. Applicants argue that the prophetic examples of the specification provides more

than sufficient guidance to enable one of ordinarily skilled in the art to use the claimed administration methods *in vivo*. Applicants point the Examiner to Examples 2-5 found in the instant specification, which teach prophetic examples of delivering and administering siRNA *in vivo*.

Applicant's arguments have been fully considered but are not found persuasive. While the Examiner agrees that MPEP 608.01(p) permits prophetic examples to support the application and claims, the test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosures in the specification coupled with the information known in the art, without undue experimentation. See In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). In the instant case, the scope of the disclosure is not commensurate with the scope of protection sought by the claims (MPEP § 2164.08). The instant specification fails to teach one of skill how to use siRNA to reliably inhibit the human ICAM-1 gene *in vivo* in any cell in any animal without undue experimentation. In light of the unpredictability associated with using and delivering siRNA *in vivo*, one of skill would be left to empirical, trial and error testing to find the appropriate conditions and materials necessary to reduce the expression of the human ICAM-1 gene in a subject *in vivo,* as instantly claimed.

Further, the MPEP, at 2164.02 also requires a correlation between *in vitro* and *in vivo* examples. In short, MPEP 2164.02 discloses:

> "An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples.""

In the instant case, a review of the instant application finds working examples directed to the inhibition of human ICAM-1 expression and cytotoxicity profiles in HEK 293 (*in vitro*) following the administration of siRNAs targeted to human ICAM-1. However, the instant claims are drawn to both methods of inhibiting human ICAM-1 in a subject (*in vivo*) and methods of treating complications arising from type I diabetes in a subject (*in vivo*) comprising the administration of a siRNA targeted to human ICAM-1. As the previous references of Lu et al., Samarsky et al., and Downward et al. indicate, cell culture results are not readily extrapolated to *in vivo* applications. Further, the HEK 293 cell culture system is not an art-recognized correlative model of type I diabetes. Thus, Applicants provide working examples in the form of *in vitro* cell culture data, where no correlation to an *in vivo* environment can be established. The Examiner would like to note that working examples are, of course, not an absolute requirement for enablement, but are a legitimate factor in determining lack of enablement. See In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). The need for additional experimentation, as in routine experimentation, is not an absolute bar to enablement, as long as the required experimentation is not undue. In all, the Wands factors have been weighed and favor undue experimentation. Because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery of siRNA, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Thus, it is maintained that the prior art at the time of Applicants' filing would not

enable the use of *in vitro* siRNA inhibition techniques to support claims directed to the *in vivo* use of siRNA, let alone claims directed to therapeutic use *in vivo*. Accordingly, one skilled in the art, being unable to use the prior art for such guidance, must necessarily find such guidance from the specification. However, one of skill would not find the guidance provided in the specification in the form of *in vitro* examples and broad prophetic treatment regimens enough to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references of Lu et al., Samarsky et al., and Downward et al. This is particularly true in view of the fact that the specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery of the siRNA.

The Examiner would like to point out that during the Interview conducted on January 16, 2007, to refute the instant rejection, it was agreed that Applicants would supply the Examiner with a declaration showing *in vivo* data. In Applicant's response filed February 26, 2007, no such declaration was filed.

In summary, because of the lack of predictability of the art, and the specification lack of particular guidance or particular direction which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery of the siRNA, undue experimentation would be required of one of skill in the art to make and use the invention as claimed. Therefore, claims 32-59 and 75-77 remain rejected and newly submitted claims 78-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is 571-272-0758. The examiner can normally be reached on 9 am - 5 pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information

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tcg
May 6, 2007

Sean McGarry
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